REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS AND AMENDMENTS

Claims 32-39 were pending in this application when last examined.

Claims 32-38 were examined on the merits and stand rejected.

Claim 39 was withdrawn as non-elected subject matter. Applicants reserve the right to file a continuation or divisional application on any canceled subject matter.

In order to expedite allowance, claim 32 is amended to reduce the scope of the claimed IP-10 variants. Support for the range of "1 to 80" can be found on page 35, lines 27-37, of the specification as filed. Support for "wherein said stringent conditions are defined as a sodium content of 19 mM and a temperature of 60°C" can be found on page 27, lines 23-27, of the specification as filed. Support for "95% homology" can be found on page 23, lines 7-14, of the specification as filed.

Claim 34 is canceled without prejudice or disclaimer thereto.

Claim 38 is amended to conform with amended claim 32.

No new matter has been added.

II. SEQUENCE LISTING

Foregoing amendments to the specification and Sequence Listing are presented to place the application in compliance with the Sequence Rules under 37 C.F.R. § 1.821-1.825.

Enclosed herewith is a substitute Sequence Listing in both paper and computer readable form as required by 37 C.F.R. § 1.821(c) and (e). Amendments directing its entry into the specification have also been incorporated herein. The content of the paper and computer readable copies are the same and no new matter has been added.

The substitute Sequence Listing lists all the sequences disclosed in the specification of four or more amino acids or of 10 or more nucleotides. The substitute Sequence Listing has been

run through the PTO Checker software (version 4.4.0) and no errors were found.

Applicants further note that the legends for Figures 1 and 2 on page 18, as well as pages 69, 87 and 90 have been amended to recite SEQ ID NOS. No new matter has been added to the specification.

In view of the foregoing, the application is now in compliance with the Sequence Rules under 37 C.F.R. § 1.821-1.825.

III. INDEFINITENESS REJECTION

Claims 32 and 34 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite on pages 3 and 4 of the Office Action. Applicants respectfully traverse this rejection.

In particular, Applicants note that the term stringent has been defined with particular conditions. Applicants further note that "essentially equal or equivalent to" has been deleted in order to expedite allowance. Finally, Applicants note that claim 32 has been amended to more clearly recite the meaning of "thereof". Thus, Applicants submit that this rejection is untenable, as applied to the amended claims, and should be withdrawn.

IV. ENABLEMENT AND WRITTEN DESCRIPTION REJECTION

On pages 4-8 of the Office Action, claims 32-38 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification is enabled for methods of administering mammalian IP-10 protein for therapeutically treating (1) a female subject to promote conceptus implantation or (2) any subject to chemoattract monocytes or lymphocytes, but not for the methods as broadly claimed, including prophylactic treatment or administration of IP-10 variants.

Also, on pages 8-11, claims 32-38 were rejected under 35 U.S.C. § 112, first paragraph, for non compliance with the written description requirement for the variety of IP-10 proteins and variants.

Applicants respectfully traverse these rejections as applied to the amended claims.

Applicants note that the scope of claim 32 has been reduced in order to expedite allowance. In particular, Applicants note that IP-10 protein variants have been limited to substitution of 1 to 80 amino acids, 95% or greater homology, or particularly defined stringent

conditions. Further, Applicants note that the IP-10 protein variants have been limited to having a biological activity of intact IP-10 protein. Applicants also note prophylaxis has been removed from the claims.

Applicants also note that the test for sufficiency of enablement is that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. As noted above, the claimed invention has been limited in order to expedite allowance. Applicants respectfully contend that this smaller scope of variants can be practiced by the skilled artisan without undue experimentation. Applicants further note that the scope of variants claimed in light of the specification and the teachings in the art reasonably convey to an artisan that the inventor had possession at the time of filing of the subject matter which is claimed. Thus, Applicants suggest that these enablement and written description rejections are untenable as applied to the variants and should be withdrawn.

Further, Applicants note that in the enablement rejection the Examiner contended that implantation of a conceptus into the uterine wall plays only one small role in the larger concepts of pregnancy, fertility/sterility, interactions between conceptus and maternal systems, immunocyte migration and immune function of the uterus. However, Applicants note that the enablement requirement merely requires that the specification teaches a skilled artisan how to make and use the claimed invention. Thus, Applicants submit that even if the claimed method does not treat the above-noted conditions all of the time, such is not a necessary to meet the enablement requirement. In fact, the functions of IP-10 and variants taught in the specification and the art would reasonably teach a skilled artisan how to make and use the claimed method for all of the noted uses.

As noted below and in the remarks of record, failure of implantation, which is a requirement for pregnancy, occurs to about 50% of fertilized eggs. Thus, increasing the rate of implantation by the claimed method will treat fertility/sterility issues, interactions between conceptus and maternal systems and pregnancy. Further, as noted previously and below, IP-10 in cell culture stimulates migration of trophoblast cells (which are associated with the placenta), increases CXCR3 receptor expression in trophoblast cells, elevates trophoblast adhesion to endometrium, elevates integrin expression in trophoblasts, is involved with NK cell migration in

the presence of progesterone, and stimulates IL-10 expression in NK cells which is essential to pregnancy.

Therefore, a person of skill in the art would understand that the claimed method is enabled for treating a subject to activate conceptus migration, promote conceptus implantation on the uterine wall, treat sterility, promote pregnancy, control interaction between conceptus and maternal system, activate immunocyte migration, and/or control immune function in the uterus without undue experimentation.

Thus, Applicants suggest that this enablement requirement is untenable and should be withdrawn.

V. NEW MATTER REJECTION

On page 8, claims 32-38 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the term "prophylactic treatment" is new matter. This term has been deleted and therefore this rejection is moot.

VI. OBVIOUSNESS REJECTION

On page 11 of the Office Action, claims 32-38 were rejected under 35 U.S.C. § 103(a) as obvious over Terao et al. (US 6,013,252) in view of Luster et al. (Molecular and Cellular Biology, Vol 7, no. 10, pp. 3723-3731, 1987).

Applicants respectfully traverse this rejection as applied to the amended claims.

In particular, Applicants note that the primary reference, US 6,013,252, is directed toward a method of promoting conception by administering IL-8 or MCAF. Applicants further note that the paragraph bridging columns 5 and 6 of this patent is directed towards promotion of fertilized-ovum implantation with IL-8 or chemokines analogous thereto. Applicants further note that the authors in this paragraph indicate that IP-10 is analogous to IL-8. Applicants strongly disagree with this assertion.

In fact, Human IP-10 is completely different from Human IL8 in view of amino acid sequence levels and biological functions as follows:

Human IP-10

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          10         20         30         40         50         60
MNQTAILICC LIFLTLSGIQ GVPLSRTVRC TCISISNQPV NPRSLEKLEI IPASQFCPRV

          70         80         90
EIIATMKKKG EKRCLNPESK AIKNLLKAVS KERSKRSP
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Function

1) Chemotactic for monocytes and T-lymphocytes.

2) IP-10 does not bind to receptor CXCR1 or CXCR2, while rather it binds to CXCR3.

3) A key mediator of the interferon gamma response.

Human IL8

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          10         20         30         40         50
MTSKLAVALL AAFLISAALC EGAVLPRSAK ELRCQCIKTY SKPFHPKFIK

          60         70         80         90
ELRVIESGPH CANTEIIVKL SDGRELCLDP KENWVQRVVE KFLKRAENS
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Function

1) Lymphocyte-derived neutrophil-activating factor

2) IL-8 is a chemotactic factor that attracts neutrophils, basophils, and T-cells, but not monocytes. It is also involved in neutrophil activation. It is released from several cell types in response to an inflammatory stimulus.

3) IL-8 binds to receptors CXCR1 and CXCR2, while does not bind to CXCR3.

Thus, a person of skill in the art would understand that IP-10 is not equivalent to IL-8 and would not be taught or suggested by the cited references that IP-10 is useful for promoting conception. Therefore, Applicants submit this rejection is untenable and should be withdrawn.

Furthermore, the present invention is based on the novel finding that IP-10 activates embryo implantation in the mother. As such, the Applicants have succeeded in finding that IP-10

promotes embryo implantation to a mother. The claims set forth in the present application are based on this novel finding.

At present, it is reported that only about 50% of fertilized eggs are successfully implanted, and pregnancy depends on this percent implantation. By using the present invention, it is now possible to increase embryo implantation rates, resulting in up to 2-fold increase in pregnancy.

Thus, it is respectfully submitted that the claimed invention is neither disclosed nor suggested by the cited references.

In addition, Applicants wish to again note the following unique new findings on which the present invention is based.

For chemokine IP-10, recombinant IP-10 proteins have the following actions at a dose of 20ng/ml under cell culture conditions:

Action 1 - Chemokine IP-10 stimulates a 1.5 to 2-fold increase in the migration of trophoblast cells.

Action 2 - Chemokine IP-10 induces about a 20-fold increase of specific chemokine receptor CXCR3 (IP-10 receptor) expression in trophoblast cells.

Action 3 - Chemokine IP-10 elevates trophoblast cell adhesion to endometrium by 2- to 3-fold.

Action 4 - Chemokine IP-10 induces a 2- to 3-fold increase in the expression of integrins (integrin α_5, α_v and β_3) in trophoblast cells. This elevated integrin expression causes an increase in the adhesion of trophoblast cells to uterine epithelial cells. It is believed that this adhesion takes place depending on the extracellular matrix (fibronectin) on the uterine epithelial cell (please note fibronectin is a substrate for the fibronectin receptor, integrin). Actually, when conceptus trophoblast cells were incubated with fibronectin, adhesiveness on day 17 (implantation initiation) and day 20 was elevated by about 5-fold and about 7-fold, respectively, as compared with that on day 14.

Action 5 - IP-10 is involved with the migration of NK cells in the presence of the pregnancy hormone (progesterone).

Further, IP-10 facilitates the expression of interleukin 10 (IL-10) (essential for establishment of pregnancy) from NK cells.

It is respectfully submitted that the cited prior art fails to disclose or suggest the above-noted unique aspects of the present invention.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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